PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/14

A1

(11) International Publication Number: WO 97/14407

(43) International Publication Date: 24 April 1997 (24.04.97)

(21) International Application Number: PCT/US96/16841

(22) International Filing Date: 17 October 1996 (17.10.96)

(30) Priority Data:
60/005,340 17 October 1995 (17.10.95) US

(71) Applicants *(for all designated States except US)*: RESEARCH TRIANGLE PHARMACEUTICALS [US/US]; Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM [US/US]; 201 West 7th Street, Austin, TX 78701 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HENRIKSEN, Inge, B. [NO/US]; Research Triangle Pharmaceuticals, Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). MISHRA, Awadesh, K. [IN/US]; Research Triangle Pharmaceuticals, Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). PACE, Gary, W. [US/US]; Research Triangle Pharmaceuticals, Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). JOHNSTON, Keith, P. [US/US]; University of Texas, Dept. Chemical Engineering, 26th and Speedway, Austin, TX 78712-1062 (US). MAWSON, Simon [US/US]; University of Texas, Dept. Chemical Engineering, 26th and Speedway, Austin, TX 78712-1062 (US).

(74) Agent: CRAWFORD, Arthur, R.; Nixon & Vanderhye P.C., 8th floor, 1100 North Glebe Road, Arlington, VA 22201-4714 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INSOLUBLE DRUG DELIVERY

(57) Abstract

Particles of water insoluble biologically active compounds, particularly water-insoluble drugs, with an average size of 100 nm to about 300 nm, are prepared by dissolving the compound in a solution then spraying the solution into compressed gaz, liquid or supercritical fluid in the presence of appropriate surface modifiers.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

WHAT IS CLAIMED IS:

1. A process of preparing microparticles up to 300 nm in size of water-insoluble or substantially water-insoluble biologically active compounds comprising the steps of :

(1) dissolving a water-insoluble or substantially water-insoluble biologically active compound in a solvent therefor to form a solution; and

(2) spraying the solution prepared in step (1) into a compressed gas, liquid or supercritical fluid in the presence of a surface modifier dispersed or dissolved in an aqueous phase.

2. A process of preparing microparticles up to 300 nm in size of a water-insoluble or substantially water-insoluble biologically active compound comprising the steps of:

(1) dissolving a water-insoluble or substantially water-insoluble biologically active compound in a compressed fluid;

(2) preparing an aqueous phase containing a surface modifier active at the compound-water interface; and

(3) spraying the compressed fluid of step (1) into the aqueous phase of step (2) to form microparticles of the compound.

3. The process according to claim 1 or 2, including the additional step of recovering the microparticles so produced.

4. The process according to claim 1 or 2, wherein the surface modifier is a phospholipid.

5. The process according to claim 1 or 2, wherein the surface modifier is a surfactant.

6. The process according to claim 1 or 2, wherein the surface modifier is a mixture of two or more surfactants.

7. The process according to claim 1 or 2, wherein the surface modifier is at least one surfactant devoid or substantially completely devoid of phospholipids.

8. The process of claim 1 or claim 2 wherein the surface modifier is a polyoxyethylene sorbitan fatty acid ester, a block copolymer of ethylene oxide and propylene oxide, a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine, an alkyl aryl polyether sulfonate, polyethylene glycol, hydroxy propylmethylcellulose, sodium dodecylsulfate, sodium deoxycholate, cetyltrimethylammonium bromide or combinations thereof.

9. The process of claim 1 or 2 wherein the surface modifier is of egg or plant phospholipid or semisynthetic or synthetic in partly or fully hydrogenated or in a desalted or salt phospholipid such as phosphatidylcholine, phospholipon 90H or dimyristoyl phosphatidylglyerol sodium salt, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, lysophospholipids or combinations thereof.

10. The process of claim 1 or 2 wherein the compound is a cyclosporine, indomethacin, or tetracaine.

11. The process of claim 1 or 2 wherein the particles are less than 100 nm in size.

12. The process of claim 1 or 2 wherein the particles range from 5 up to about 50 nm in size.

13. The process of claim 1 or 2 wherein 99% of the particles produced are below 500 nm.

14. The process of claim 1 or 2 wherein 99% of the particles produced are below 400 nm with peaks at half width at half height at about 200 nm.

15. The process of claim 14 when the peaks are below 100 nm.

16. The process of claim 1 or 2 wherein the compressed gas or fluid is gas, liquid or supercritical carbon dioxide.

17. The process according to claim 2, wherein the compressed fluid sprayed in step (3) is sprayed through a capillary orifice.